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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Brent R. Stockwell et al.	Confirm. No.:	6924
Serial No.:	09/611,835	Art Unit:	1639
Filed:	July 7, 2000	Examiner:	Jeffrey S. Lundgren
Customer No.:	21559		
Title:	METHODS FOR IDENTIFYING COMBINATIONS OF ENTITIES AS THERAPEUTICS		

Board of Patent Appeals and Interferences
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

REQUEST FOR REHEARING

Pursuant to 37 C.F.R. § 41.52, appellants respectfully request that the proceeding be reheard by the Board.

REMARKS

Summary of Decision on Appeal

In its April 20, 2007 decision, the Board reversed the Examiner's rejection of claims 89-156 for obviousness, but set forth a new rejection of claims 89-156 under 35 U.S.C. § 103(a) over several prior art references, most notably Stylli, West, Burgin, and Chiang. Appellants respectfully request reconsideration of this new rejection.

Claim Construction

As an initial matter, appellants respectfully submit that the Board misconstrued claim 89, which reads:

> 89. A method of discovering a desired two or higher order combination of compounds having the ability to affect a biological property of living cells in a way that is indicative of the potential for therapeutic efficacy in an animal, said method comprising the steps of:
>
> (a) providing at least forty-nine unique combinations of at least seven different compounds,
>
> (b) contacting each unique combination with living test cells under conditions that ensure that each contacting is segregated from the others,
>
> (c) measuring or detecting said biological property of the test cells as an indication of the effect of each combination on the test cells,
>
> (d) identifying combinations of compounds that have an effect on a property of the test cells that is indicative of the potential for therapeutic efficacy in an animal, and
>
> (e) at any time during said method, contacting each compound in the combination identified in step (d) with said living test cells and thereafter measuring or detecting said biological property of the test cells as an indication of the effect of each compound on the test cells, wherein the combination identified in step (d) constitutes said desired combination if the effect of the combination on said biological property of the test cells is greater than the effect of each compound, individually, on said biological property of the test cells.

The Board stated that "[b]ecause step (e) requires that (d) first be performed, we interpret 'at any time during said method' to mean at any time after step (d) has been performed."

The Board is incorrect in stating that step (d) must be performed prior to step (e). In fact, as is demonstrated in the following hypothetical example, step (e) can be performed first. In this example, one hundred individual compounds are each tested for activity against test cells. Their level of activity is measured and recorded. Subsequent to the testing of the individual compounds, pair-wise combinations of two compounds are then tested for activity, and the level of activity of each pair is measured and recorded. The activity of the pair-wise combinations is then compared to that of the individual constituent compounds to identify those combinations having an effect on the biological property of the test cells that is greater than the effect of each compound, individually.

As is clear from this example, each compound is tested individually before it is tested in pairwise combinations. In other words, step (e) is performed prior to step (d). This example unambiguously demonstrates that the Board's conclusion that "step (e) requires that (d) first be performed" is incorrect. Reconsideration is respectfully requested.

Rejection under 35 U.S.C. § 103(a)

Appellants now turn to the Board's new ground of rejection of claims 89-156. For clarity, appellants first address claims 154-156, and then address the remaining claims.

Claims 154-156

Claim 154-156 are directed to appellants' so-called "rank order" screening method. In this method, which is described in the specification on page 6, lines 21-27, through page 7, lines 1-6, before combinations are tested, at least 100 compounds are tested individually for activity against test cells. Compounds that

demonstrate activity individually are then tested as large numbers of combinations. For the Board's convenience, claim 154 is reproduced below.

> 154. A method of discovering a desired two or higher order combination of compounds having the ability to affect a biological property of living cells in a way that is indicative of the potential for therapeutic efficacy in an animal, said method comprising the steps of:
>
> (a) contacting living test cells with at least 100 compounds under conditions that ensure that each compound/test cell contacting is segregated from the others,
>
> (b) detecting or measuring a biological property of said test cells,
>
> (c) selecting compounds that cause a change in said biological property relative to said biological property of said test cells not contacted with said compounds,
>
> (d) contacting at least 49 unique two or higher order combinations of the selected compounds of step (c) with living test cells under conditions that ensure that each contacting is segregated from the others,
>
> (e) detecting or measuring a biological property of said test cells of step (d), and
>
> (f) identifying combinations of compounds that cause an effect on said biological property of said test cells that is different from the effect of each compound of the combination by itself, wherein said identified combinations of compounds have potential therapeutic use in an animal.

The Board contends that the method of claims 154-156 is unpatentable as being obvious over Stylli in view of West, Burgin, and Chiang. In its reasons supporting the rejection of claims 154-156, the Board makes no mention of the requirement in these claims that compounds be tested individually before being tested in combination. Indeed, the Board appears to overlook the fact that steps (a)-(d) of claim 154 are very different from steps (a)-(d) of the other independent claims: the Board states that Stylli "meets the limitations of steps (a) through (d) of independent claims 89, 114, 135, 149, and 154, and dependent claim 156." There is no explanation in the Board's decision for the Board's assertion that Stylli

teaches these steps. No could there be; there is nothing in Stylli teaching or suggesting the claimed screening method. Moreover, nothing in the references newly cited by the Board remedies the deficiencies of Stylli. West, Burgin, and Chiang each teaches a method that employs pooling of agents. Pooling is employed by researchers such as West, Burgin and Chiang in order to improve screening efficiency by eliminating the requirement that each compound be tested individually. For example, in the method described by West at column 11, lines 9-40, and relied upon by the Board, pools of one thousand potentail inhibitors are screened in wells. If a well is found to contain an inhibitor, "then the pool can be subdivided into 10 pools of 100 and the process repeated until an individual inhibitor is identified." (col. 11, ll. 46-48). Thus, using the method described by West and beginning with 10 panels of one thousand compounds, a practitioner would need test only 10 compounds individually.[1] In stark contrast, one employing the method of claim 154 would first test every compound individually to identify those that change a particular biological property. Importantly, compounds so identified are then combined after their individual activity has been discovered, a step that West and Burgin, searching for individual compounds having biological activity, do not suggest performing.

Because none of the references cited by the Board teach or suggest testing compounds individually and then testing them in combination, appellants respectfully request that the rejection of claims 154-156 as being obvious be withdrawn.

Claims 89-153

Among the remaining claims that stand rejected as being obvious are four independent claims—claims 89, 114, 135, and 149. While these claims include

[1] The teachings of Burgin and Chiang are similar to those of West, and provide no support for the Board's position that claims 154-156 are unpatentable as being obvious.

different claim limitations, for the purposes of determining patentability, the Board has treated them as a group and appellants treat them similarly below.

The Board summarizes the claims as being directed to "a method of screening combinations of compounds which affect a biological property of living cells." Appellants respectfully submit that this characterization of the claims is inaccurate, and that the claims are more specific than that. As is clear from the preamble of claim 89, reproduced above, and which the other independent claims share, the claims are directed to methods of discovering a desired two or higher order combination of compounds having the ability to affect a biological property of living cells in a way that is indicative of the potential for therapeutic efficacy in an animal. In other words, claims 89, 114, 135, and 149 are not directed to combination screening for the purpose of identifying individual compounds having a desired activity. Rather, these claims are directed to methods for identifying combinations of drugs having therapeutic potential. While compounds are also tested individually, the purpose is to determine whether the activity observed in the combination can be ascribed to a single drug constituent of the combination.

As the Board stated, West, Burgin, and Chiang teach a screening method in which compounds are pooled. Pooling is performed to more efficiently screen a large number of compounds for individual compounds having a desired activity. The method of claims 89, 114, 135, and 149 cannot be characterized as encompassing pooling. The difference between the method of claims 89, 114, 135, and 149 and the pooling method of the prior art can be demonstrated in a hypothetical example, in which two compounds ("A" and "B") are tested for their ability to inhibit cell proliferation. In this example, a score of 2 represents a robust inhibition, while a score of 1 represents no inhibition. The results of this hypothetical screen are as follows.

Compound	Score
A + B	2
A	1
B	1
Vehicle control	1

In this hypothetical assay, inhibition was observed when compounds A and B were both present, but was not observed when each compound was tested individually. For the prior art, this result is a failure, for the present inventors, it is the result they hoped for; the combination of compounds A and B is potentially a therapeutic. Thus, unlike in the methods of the invention, in the prior art pooling assays, the loss of activity when compounds A and B are separated produces an unsatisfying result for the researcher, whose purpose is to identify individual compounds having a desired activity (see col. 11, ll. 46-48 of West: "the pool can be subdivided into 10 pools of 100 and the process repeated until an individual inhibitor is identified").

Adding Stylli to the pooling references does nothing to move those references closer to the claimed invention. Even if one in the field of compound screening would consider applying the pooling strategy of West, Burgin, and Chiang to Stylli's automated screening method, but the goal would be the same—to identify individual compounds having activity. Quite simply, there is nothing in any of the references relied upon by the Board that suggests screening large numbers of combinations of compounds to identify combinations having therapeutic potential. For this reason, *inter alia*, reconsideration of the rejection of claims 89-153 as being obvious is respectfully requested.

Conclusion

For all of the reasons given above, it is respectfully requested that the rejection of all of the claims be reversed. If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: 6/20/07

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